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FREE-RADICAL ANNELATION IN THE SYNTHESIS OF BICYCLIC β-LACTAMS. 5.[1] SYNTHESIS OF CARBAPENAMS

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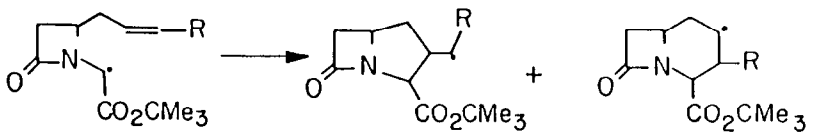
Summary: Homolytic cyclization of some alkenyl β-lactams afforded carbapenams, by *exo* addition, when a vicinally disubstituted double double bond was involved, and carbacephams, by *endo* addition, when a terminal double bond was involved.

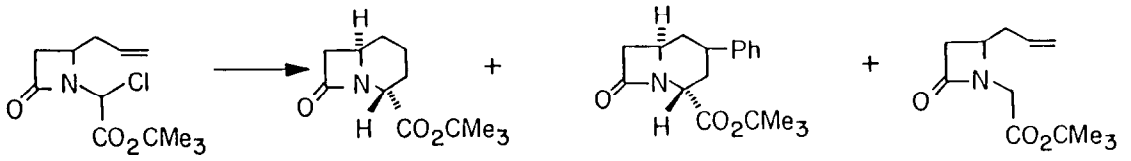
Some years ago, we described the synthesis of the (±)-1-oxacepham and (±)-1-oxahomocepham systems.[1] The key reaction in that synthesis involved the completion of the bicyclic β-lactam backbone through the intramolecular addition of a carbon-centered free radical to a carbon-carbon multiple bond. This process which followed the 6-*exo* addition mode in the first case, and the 7-*endo* addition mode in the second, did not involve the introduction of a substantial strain in the molecule. We now describe the application of a similar free radical annelation for the construction of the highly strained carbapenam system.[2] The interest in carbapenams remains in their structural similarity to the thienamycin-type antibiotics which derive from the unsaturated Δ^2-carbapenam system.[3]



1 2 3

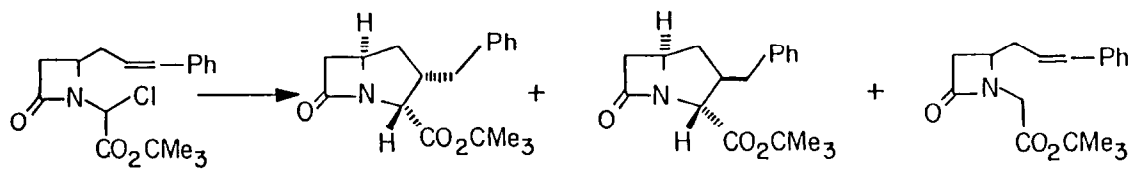
Our synthetic strategy is based on the synthesis of nonfused β-lactams which may be induced to generate free radicals of type **1**. Free radicals **1** may cyclize through the 5-*exo* mode to give carbapenam-carbinyl radicals **2**, or through the 6-*endo* mode to give carbacepham radicals **3**. As precursors of free radicals of type **1**, we chose the chlorides **4** and **8**, which were prepared from 4-allylazetidin-2-one[4] by conventional methods.[5] When the chloride **4** was treated with tri-n-butylstannane (1.1 equivalent) and

azobisisobutyronitrile (AIBN) (5 molar %) in boiling benzene (0.02M solution), the nonfused β-lactam **7**[8], deriving from direct hydrogen transfer to the parent free radical **1**, was obtained as the major product (50%), while the carbacepham **5**[8] accounted for only 20% yield. The product ratio was, however, inverted when the reaction was performed under high dilution conditions. Thus, simultaneous addition of individual solutions of tri-n-butylstannane (1.1 equivalent) and AIBN (3 molar %) in benzene, during 90 min, to a boiling solution of the chloride **4** in benzene (0.003M), resulted in a nearly quantitative conversion of the starting material into a mixture of the carbacepham **5**, the 2-phenylcarbacepham **6** and the nonfused β-lactam **7** in a ratio of 6.8:2.2:1;[9] the isolated yields of the product were, respectively, 50%, 14% and 5%. The carbacephams **5** and **6** were obtained from the same intermediate radical **3** (R = H), the former by hydrogen transfer and the latter by homolytic substitution on benzene, which was used as solvent. No carbapenam, which would derive from *exo*-cyclization involving radical **2** (R = H) was detected.



4 5 6 7

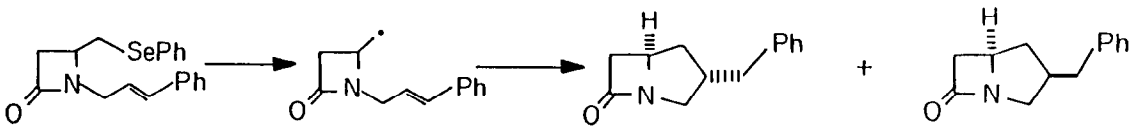
This exclusive *endo*-cyclization seems to be typical of azetidin-2-ones bearing a free radical, centered either at position-4[10,11], or on the N-exocyclic carbon atom[1] when added to a terminal double bond.[12] However, as expected,[1] annelation occurs exclusively through the *exo* mode when the radical adds to a substituted multiple bond. Thus, treatment of the chloride **8**[5] (0.02M solution in benzene) with tri-n-butylstannane (1.1 equivalent) and AIBN (5 molar %) for 90 min at 80°C afforded (nearly quantitatively) a mixture of the carbapenams **9**[8] and **10**[8], and the nonfused β-lactam **11**, in a ratio of 1.9:1.7:1, respectively.[9] The isolated yields were 62% for the carbapenams **9** and **10**, and 20% for β-lactam **11**.



8 9 10 11

The ratio of annelated-bicyclic β-lactam to nonfused β-lactam can be further increased by augmenting the reactivity of the radical center involved in the intramolecular addition. For example, the 4-phenylselenomethylazetidin-2-one **12**[14] (0.007M solution in benzene) was converted (80%)[9] into the 2-benzylcarbapenams **14**[8] and **15**[8] (1:1.8 ratio) on treatment with tri-n-butylstannane (1.1 equivalent) and

AIBN (5 molar %) at 80°C No products derived from direct hydrogen transfer to the intermediate free radical **13** or from its *endo* cyclization were detected.



12 13 14 15

It is noteworthy that in addition to the high regioselectivity observed in all the cyclizations described above, the annelations of the nonfused β-lactams **4** and **8** are also highly stereoselective with respect to the relative configuration between the ester group and the bridgehead hydrogen atom. In fact, the relative configuration of carbon-3 versus carbon-5 of the carbapenams **9** and **10** is the same as that observed in the natural penicillins and in clavulanic acid.

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2. For other syntheses of derivatives of carbapenam-3-carboxylic acid, see, for example:Bachi, M.D.; Breiman, R.; Meshulam, H. *J. Org. Chem.* **1983**, *48*, 1439. Barrett, A.G.M.; Graboski, G.G.; Russell, M.A. *J. Org. Chem.* **1985**, *50*, 2603. Dumas, F.; d'Angelo, J. *Tetrahedron Lett.* **1986**, *27*, 3725, and references cited therein.

3. For reviews see: Ratcliffe, R.W.; Albers-Schönberg, G. in "Chemistry and Biology of β-Lactam Antibiotics", Morin, R.B. and Gorman, M., Eds. Academic Press 1982, Vol 2, p.227. Kametani, T. *Heterocycles* **1982**, *17*, (special suppl.), 463. Southgate, R.; Elson, S. *Progr. Chem. Org. Nat. Prod.* **1985**, *47*, 1.

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5. 2-Oxazetidin-1-yl(chloro)acetates **4** and **8** were prepared from the corresponding N-unsubstituted azetidin-2-ones according to Scartazzini *et al.*[6] 4-Phenyl- allylazetidin-2-one was prepared by oxidation of 4-allylazetidin-2-one[4] according to Takano *et al*,[7] followed by condensation of the corresponding aldehyde with triphenylbenzylphosphorane.

6. Scartazzini, R.; Peter, H.; Bickel, H.; Heusler, K.; Woodward, R.B. *Helv. Chim. Acta* **1972**, *55*, 408.

7. Takano, S.; Kasahara, C.; Ogasawara, K. *Chemistry Lett.* **1982**, 631.

8. a) All new compounds gave IR, ^{1}H NMR and elemental or high resolution MS analyses consistent with the assigned structures.
b)Selected spectral data, **5**: ν (film) 1751, 1734cm^{-1}; δ (CD_2Cl_2) 2.54(dd,J=14.5, 1.9Hz, 7β-CH), 3.08(dd, J=14.5, 4.6Hz, 7α-CH), 3.63(m, 6α-CH). 4.39(d, J=6.7Hz, 4β-CH). **9**:ν (film) 1768, 1734cm^{-1}; δ (CD_2Cl_2) 2.61(dd, J=15.6, 1.8Hz, 6β-CH), 2.71(dd, J=13.1, 9.1Hz, CHCH**H**(H)Ph), 3.10(dd, J=13.1, 5.2Hz, CHCH**H**(H)Ph), 3.22(dd, J=15.6, 4.7Hz, 6α-CH), 3.76(m, 5α-CH), 3.93(d, J=8.2Hz, 3β-CH). **10**:ν (film) 1768, 1734cm^{-1}; δ (CD_2Cl_2) 2.45(dd, J=13.0, 9.8Hz, CHCH**H**(H)Ph), 2.64(dd, J=16.2, 2.9Hz, 6β-CH), 2.93(dd, J=13.0, 4.9Hz, CHCH**H**(H)Ph), 3.29(dd, J=16.2, 5.5Hz, 6α-CH), 4.04(m, 5α-CH), 4.43(d, J=7.1Hz, 3β-CH).

9. Determined by ^{1}H NMR spectra.

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12. Cyclizations of some dialkenylazetidin-2-ones involving vinyl radicals followed both *endo* and *exo* modes.[13]

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14. β-Lactam **12** was prepared from cinnamyl bromide and 4-phenylselenomethylazetidin-2-one. The latter was obtained from 4-iodomethylazetidin-one[15] and PhSe(BH_3)Na.

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